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Original citation:
Coe, Samuel, Pereira, Nicole, Geden, Joanna V., Clarkson, Guy J., Fox, David J., Napier, Richard M. , Neve, Paul and Shipman, Michael. (2015) Ring closing metathesis reactions of α-methylene-β-lactams : application to the synthesis of a simplified phyllostictine analogue with herbicidal activity. Organic & Biomolecular Chemistry, Volume 13 (Number 28). pp. 7655-7663.

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http://dx.doi.org/10.1039/C5OB00890E

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Ring Closing Metathesis Reactions of α-Methylene-β-Lactams: Application to the Synthesis of a Simplified Phyllostictine Analogue with Herbicidal Activity†

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Ring closing metathesis (RCM) reactions of α-methylene-β-lactams are used to construct strained 11- and 12-membered macrocycles that mimic key structural elements of phyllostictine A. The highest yield and stereoselectivity was achieved making 12-membered macrocycle *Z*-**19** with use of a *p*-methoxyphenyl group on the lactam nitrogen. Interestingly, substrate concentration had an important influence on the stereochemical course of the reaction. A simplified analogue produced using this approach displays phytotoxic activity against *Chlamydomonas reinhardtii* suggesting that the α-methylene-β-lactam subunit is responsible, at least in part, for the herbicidal activity of phyllostictine A.

Introduction

There is an urgent need to find new herbicides with novel mechanisms of action to address the growing levels of resistance evolving against the chemicals currently used in agriculture.[1] The structural diversity and biological activity of natural products offers tremendous opportunities for the development of new agents based on the compounds themselves or synthetic herbicides derived from these natural phytotoxins.[2] In 2008, Evidente *et al.* reported the isolation and structural elucidation of a new class of natural herbicide produced by the fungus *Phyllosticta cirsii.*[3] Four new compounds named phyllostictines A-D (**1**-**4**) based upon a unique oxazatricycloalkenone skeleton were identified (Figure 1). Members of the phyllostictine family show variation in the size of the lactam and carbocyclic rings, the nature of the substituent at C–5, and the level of oxidation. Alongside their unique chemical architectures, the phyllostictines have been shown to exhibit significant activity as herbicides. The most potent member of the family, phyllostictine A (**1**) displays considerable efficacy against thistles in both leaf puncture and isolated protoplast assays.[4] Phyllostictine A is more potent than fusaric acid, a well-known and powerful toxin, and faster acting than glyphosate.[4] Currently, there is only rudimentary knowledge about structure-activity relationships (SAR) within this compound class (*vide infra*), and little is known about their herbicidal mechanism of action. The discovery that phyllostictine A also possesses *in vitro* anti-cancer activity against a number of human tumour cell lines further highlights the potential value of this structurally unique class of natural product.[5]

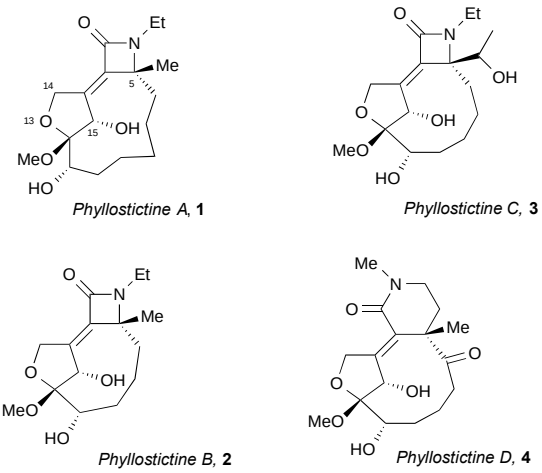
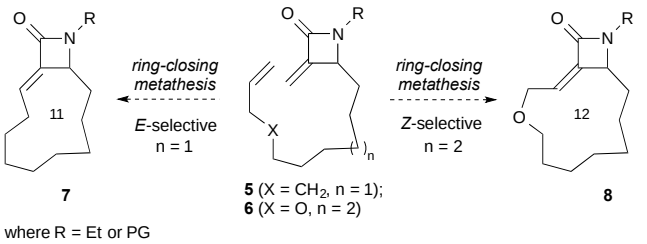


Fig. 1 Structures of the herbicidal natural products, phyllostictine A-D.

To advance our understanding of the phytotoxicity of these compounds, we sought to construct a series of simplified macrocyclic α-methylene-β-lactams through application of ring closing metathesis (RCM), and examine if such derivatives possess herbicidal activity (Scheme 1). In this manner, we would learn whether the β-lactam ring plays an important role. Moreover, RCM reactions of α-methylene-β-lactams are unprecedented and the ring strain and size of the phyllostictine A architecture provide an exceptionally demanding test for this methodology.[6] Nevertheless, we were encouraged by the work of Howell, who has shown that cross-metathesis reactions of α-methylene-β-lactams are efficient.[7] At the outset, it was unclear whether the *Z*- or *E*-isomer about the newly formed

trisubstituted double bond would be formed. Consequently, we targeted two systems requiring opposite stereochemical configurations about this alkene bond. The first required RCM of diene **5** leading to 11-membered macrocycle **7** whose backbone maps over the carbon backbone of phyllostictine A through C–15 (Figure 1). Alternatively, using ether **6**, we aimed to prepare 12-membered **8** overlaying O–13 and C–14 of the natural product (Scheme 1). Here, we describe our initial findings that establish the feasibility of making macrocyclic β-lactams by RCM, and some of the critical parameters for success with this approach.

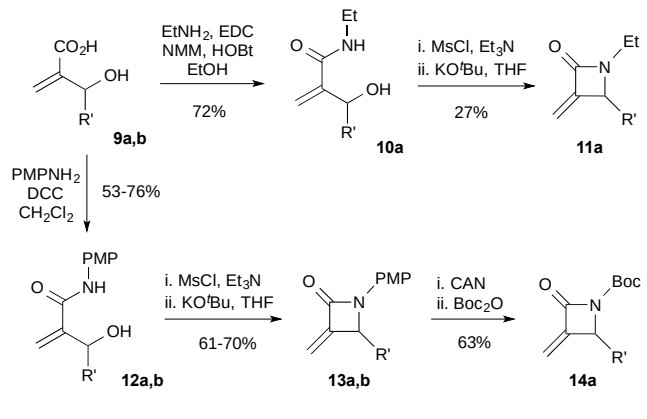


Scheme 1 Proposed RCM reactions to phyllostictine A analogues.

Results and discussion

Synthesis of RCM substrates

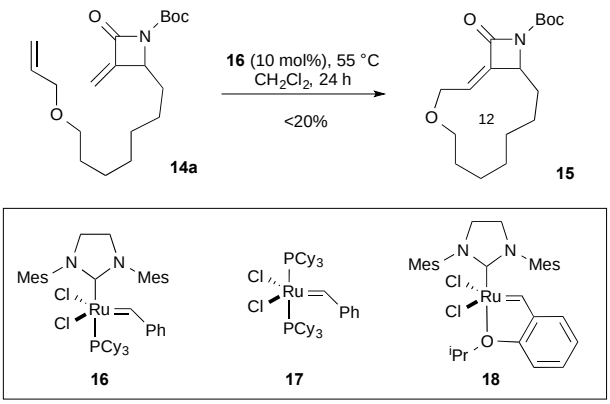
A number of methods are available for the synthesis of α-methylene-β-lactams.[8,9] Using the chemistry of Adam *et al*.[9] we prepared four RCM substrates (**11a**, **13a**,**b** and **14a**) to study the influence of tether length and nitrogen substituent on the efficiency/selectivity of the RCM (Scheme 2). The starting hydroxy acids **9a** and **9b** were made by Baylis-Hillman reaction of 8-(allyloxy)octanal[10] and 10-undecenal respectively with methyl acrylate, followed by saponification (for details, see Experimental). Using **9a,b**, amide bond formation with *p*-anisidine provided **12a,b** which could be efficiently cyclised to **13a,b** by activation of the hydroxyl group and subsequent KO^{t}Bu induced 4-*exo*-*tet* ring closure. The same approach was successfully used to make *N*-ethyl derivative **11a** albeit in modest overall yield. The Boc-protected derivative **14a** was conveniently prepared by PMP removal from **13a** and subsequent reprotection of the NH lactam with Boc anhydride.



Scheme 2 Synthesis of RCM precursors.

RCM reactions of α-methylene-β-lactams

Concerned that the formation of the smaller 11-membered macrocycle might be especially demanding,[11] our initial studies focused on RCM reactions of **6** to produce 12-membered lactam **8** (Scheme 1). To examine the impact of the electronic characteristics of the lactam ring on RCM efficiency, the reactions of **11a**, **13a** and **14a** bearing ethyl, PMP and Boc groups on the nitrogen were explored. Treatment of **11a**, bearing an *N*-ethyl group, with the versatile second-generation Grubbs catalyst (**16**) at a substrate concentration of 2 mM in CH_2Cl_2 led to complex mixtures of products from which the 12-membered macrocycle could not be isolated. Disappointingly, the use of other catalysts, namely **17** and **18**, failed to yield any improvements.[12] Treatment of Boc-protected **14a** provided slightly better results from which a low yield of macrocycle **15** could be obtained alongside quantities of the linear and cyclic dimers as evidenced by mass spectrometry (Scheme 3). These findings suggest that RCM reactions of α-methylene-β-lactams are less tolerant to changes in lactam structure than the corresponding cross-metathesis processes. Indeed, using 1-pentene as the cross-partner and **16** as catalyst, Howell has shown that both *N*-Boc and *N*-Bn α-methylene-β-lactams give cross-products in high yields.[7]



Scheme 3 Attempted RCM reactions of Boc-protected **14a**.

Greater success was achieved using PMP protected **13a**. When this lactam was treated with catalyst **16** at 2 mM substrate concentration for 24 h, the 12-membered lactam **19** was produced in 37% yield along with quantities of the macrocyclic dimer **20** (14%) (Scheme 4). Lactam **19** was formed as a 1.6:1 mixture of *Z*:*E* isomers under these conditions. Only a single diastereomer of dimer **20** was isolated as judged by ^{13}C NMR spectroscopy. Its stereochemistry, and that of *Z*-**19**, were unambiguously deduced by X-ray diffraction on single crystals grown from THF/hexane and EtOAc/hexane respectively (Figure 2).‡ To improve the yield and reduce dimer formation, the reaction was performed at higher dilution. Only a small improvement in the yield of **19** was seen (44%) along with little change in the amount of **20** (16%) when the substrate concentration was lowered 8-fold to 0.25 mM (Scheme 4).

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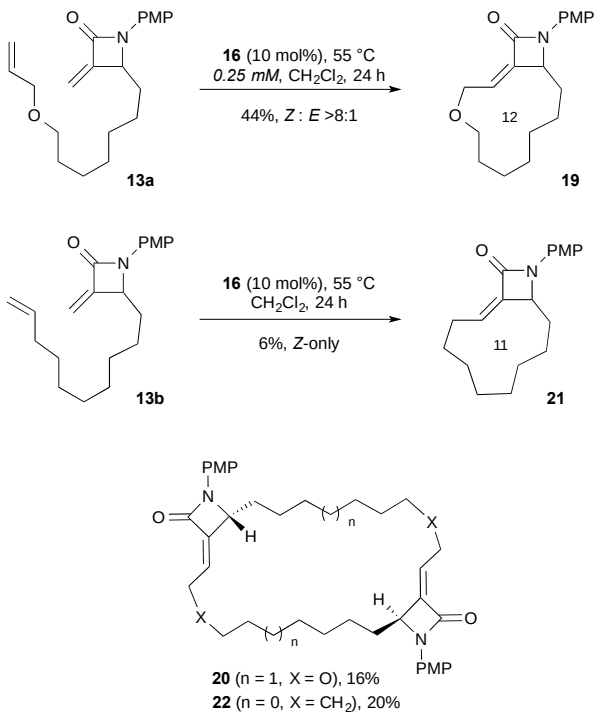
However, there was striking improvement in the stereoselectivity (*Z* : *E* >8:1).¶ This improvement could arise in a number of ways. *Z*-**19** could be formed as the kinetic product but is converted to *E*-**19** (and **20**) through reversibility in the RCM. Alternatively, *Z*- to *E*-**19** could interconvert without cleavage of the newly formed σ-bond by olefin isomerisation.[13] To explore the reversibility of the RCM reaction, purified *Z*-**19** and **20** were separately resubjected to the reaction conditions (2 mM substrate concentration, CH_2Cl_2, 40 °C, 24h). HPLC analysis revealed that *Z*-**19** equilibrated to a mixture containing *Z*- and *E*-**19** alongside **20** in a 1.3:1.2:1 ratio (see Supplementary Information). Similar behaviour was seen with **20** which partially converted to *Z*-**19** (*ca* 15%) over 24 h.



Scheme 4 Stereoselective synthesis of bicyclic α-methylene-β-lactams **19** and **21**.

Consistent with the findings, DFT structure optimisations and ZPE calculations performed at the B3LYP-D3(BJ)/SVP level followed by single point energy calculations at the B3LYP-D3(BJ)/TZVP level on *E*- and *Z*-isomers of **19** revealed that the *E*-isomer is thermodynamically more stable by only 0.9 kJ mol^{-1} (see Supplementary Information). Thus, on the basis of the available evidence, it seems probable that *Z*-**19** is kinetically favoured, but at higher concentrations the greater number of collisions with the catalyst accelerate isomerisation to mixtures of Z- and *E*-**19**, and **20**, at least in part, by regeneration of the ring-opened ruthenium carbenoid intermediate. Moreover, kinetic preference for the *Z*-isomer is fully consistent with the cross-metathesis reactions of α-methylene-β-lactams, where Howell witnessed a modest preference for this isomer when the lactam ring is substituted at C–4.[7]

Encouraged by the success achieved in the 12-membered ring series using PMP protection, we next examined the RCM reactions of **13b**. Reaction of this compound with catalyst **16** produced a 22-membered macrocyclic dimer **22** as the major product. Small quantities of *Z*-**21** were also isolated as a single geometric isomer. The structure of *Z*-**21** was confirmed by X-ray diffraction from a single crystal grown from EtOAc/hexane (see Supplementary Information).‡§

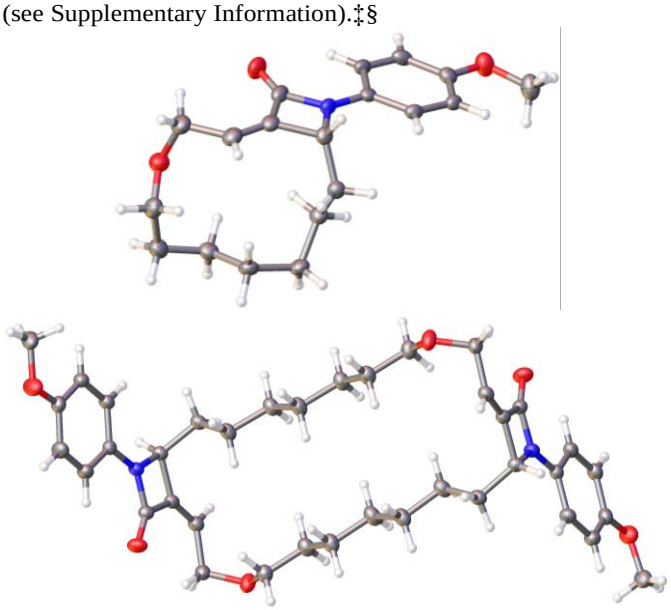
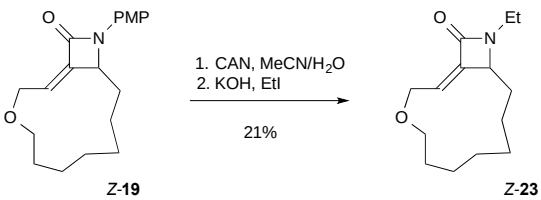


Fig. 2 Solid-state structure of **19** (top) and **20** (bottom) showing the *Z*-stereochemistry about their double bonds.

Herbicidal testing

Initial attempts to evaluate the herbicidal activity of the RCM products were severely hampered by the poor solubility of **19** in aq. DMSO. To circumvent this problem, we undertook deprotection of *Z*-**19** with ceric ammonium nitrate (CAN) in MeCN/H_2O to produce the NH lactam. This was immediately subjected to alkylation using KOH with ethyl iodide as solvent.[14] After semi-preparative HPLC, lactam *Z*-**23** was isolated in an unoptimised 21% yield over the two steps (Scheme 5). The *N*-ethyl substituent was chosen to match the structure of phyllostictine A itself. Insufficient quantities of **21** were available to undertake the same nitrogen substituent exchange in the 11-membered series.



Scheme 5 Replacement of the PMP group of *Z*-**19** to prepare a simple analogue of phyllostictine A.

Next, the growth inhibition effects of *Z*-**23** on the green alga *Chlamydomonas reinhardtii* were assessed. This unicellular organism provides a simple platform with which to evaluate

herbicidal activity.[15] Pleasingly, measurable growth inhibition of *C. reinhardtii* was observed in a dose responsive manner (Fig. 3). Glyphosate was used as a positive control in this assay. At 50 μM, the maximum dose at which *Z*-**23** remained soluble in aq. DMSO, 31±9% inhibition was observed compared to 65±5% for glyphosate.¥

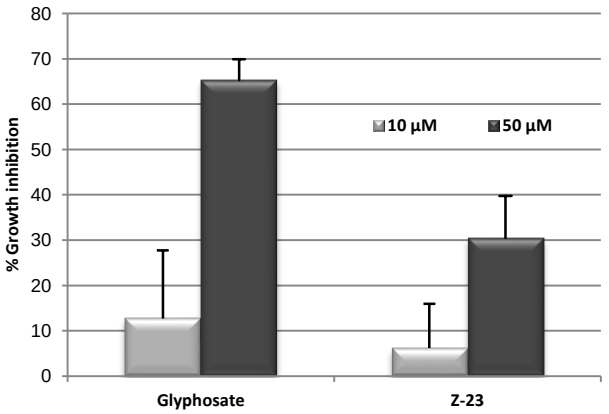


Fig 3. Growth inhibition in *Chlamydomonas reinhardtii* cultures treated with glyphosate and *Z*-**23** at 10 and 50 μM. Inhibition is calculated as percentage decrease in *Chlamydomonas* population size over 7 days (measured as OD_{750nm}) relative to control cultures treated with 0.5% (v/v) DMSO only. Bars represent averages of four replicates. Error bars are standard errors of the mean.

Conclusions

These studies show for the first time that α-methylene-β-lactams can undergo RCM reactions. The methodology provides a practical strategy for the assembly of lactam-fused, 12-membered rings in a stereocontrolled manner, provided close attention is given to the reaction conditions. Our data indicate that the reactions are reversible, with a preference for the *Z*-alkene at low substrate concentrations. Whilst we have not exhausted all available catalysts,[12] the synthesis of smaller 11-membered rings only proceeded in very low yield. In fact, the use of RCM reactions to generate this ring size is known to be challenging.[11]

Unlike cross-metathesis reactions of α-methylene-β-lactams, we observe that these macrocyclisations are very sensitive to the nature of the nitrogen substituent. The best results were achieved using the PMP group, which we show can be interchanged with other substituents post-RCM. Dimer formation is the major competing reaction with cyclic dimers **20** and **22** formed as by-products using **13a** and **13b** respectively.

The methodology provides access to new analogues of phyllostictine A. The poor solubility of our synthetic macrocyclic β-lactams in aq. DMSO precluded detailed assessment of their herbicidal activity in comparison to glyphosate, phyllostictine A or other commercial herbicides. However, our preliminary data reveal that *Z*-**23** does possess appreciable activity against *Chlamydomonas reinhardtii* at μM concentrations. Clearly, the α-methylene-β-lactam unit, the only notable functional group within *Z*-**23**, can induce phytotoxic effects. Perhaps the primary role of the other polar functionality within phyllostictine A is to aid solubility. Whether the bioactivity is associated with the strained four-membered ring, the presence of a Michael acceptor, or a combination of the two remains to be determined. However, we note that phyllostictine D, containing an unsaturated δ-lactam, does retain herbicidal activity.[4] Moreover, phytotoxic β-lactams are rare.[16] Future studies will focus on further understanding the origin and mechanism of action of these natural products, and to realising the total synthesis of phyllostictine A.

Experimental

General

Anhydrous solvents were purchased in Sure/Seal™ bottles from Sigma-Aldrich. All other solvents and reagents were used as received or purified by standard protocols. Petroleum ether refers to the fraction of petroleum ether having a boiling point between 40-60 °C. All experiments were performed under an inert atmosphere (N_2) and moisture sensitive reactions were conducted in oven- or flame-dried glassware. Flash chromatography was carried out using Matrex silica 60. Thin layer chromatography was performed on pre-coated aluminium-backed plates and developed using UV fluorescence (254 nm) and/or potassium permanganate, followed by heating. Infrared spectra were recorded neat using a PerkinElmer Spectrum One FT-IR spectrometer with internal calibration. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker DPX-300; at 400 MHz and 100 MHz respectively on a Bruker DPX-400; and at 600 MHz and 150 MHz respectively on a Bruker AV-600 spectrometer. High resolution mass spectra were obtained on a Bruker MicroTOF instrument. Melting points were recorded on a Gallenkamp MPD350 apparatus.

Methyl 10-(allyloxy)-3-hydroxy-2-methylenedecanoate (24a)

MeOH (766 μL) and DABCO (755 mg, 6.73 mmol) were added to a mixture of 8-(allyloxy)octanal[10] (5.95 g, 32.3 mmol) and methyl acrylate (2.42 mL, 26.9 mmol), and the solution was stirred at room temperature. After 2 days, and also after 5 days, additional DABCO (755 mg, 6.73 mmol) was added. After a total of 7 days, the volatiles were removed and the product was purified by column chromatography (17% EtOAc in petroleum ether) to give **24a** (4.02 g, 55%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.22 (1H, s), 5.91 (1H, ddd, *J* = 16.8, 10.6, 5.7 Hz), 5.79 (1H, s), 5.26 (1H, dd, *J* = 16.8, 1.4 Hz), 5.16 (1H, dd, *J* = 10.6, 1.4 Hz), 4.38 (1H, q, *J* = 6.4 Hz), 3.96 (2H, d, *J* = 5.7 Hz), 3.78 (3H, s), 3.41 (2H, t, *J* = 6.7 Hz), 2.54 (1H, d, *J* = 6.9 Hz), 1.68-1.61 (2H, m), 1.61-1.52 (2H, m), 1.46-1.28 (8H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 167.0 (C=O), 142.4 (C), 135.1 (CH), 125.0 (CH_2), 116.7 (CH_2), 71.9 (CH_2), 71.8 (CH), 70.5 (CH_2), 51.9 (CH_3), 36.2 (CH_2), 33.8 (CH_2), 29.4 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 24.5 (CH_2); IR (cm^{-1}): 3430,

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2931, 2857, 1717; MS-ESI: 293 $[M+Na]^+$; HRMS ES^+: $[M+Na]^+$ calcd for $C_{15}H_{26}NaO_4$, 293.1723, found 293.1721.

10-(Allyloxy)-3-hydroxy-2-methylenedecanoic acid (9a)

A solution of $LiOH·H_2O$ (3.06 g, 72.9 mmol) in H_2O (65 mL) was added to a solution of **24a** (4.02 g, 14.9 mmol) in THF (65 mL), and the mixture was stirred at room temperature for 16 h. The layers were separated, and the aqueous layer was acidified to pH 1 with 2N HCl and then extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **9a** (3.76 g, 99%) as a colourless oil which was used without further purification. ^{1}H-NMR ($CDCl_3$, 500 MHz, δ): 6.38 (1H, s), 5.91 (1H, s), 5.97-5.87 (1H, m), 5.27 (1H, dq, *J* = 17.2, 1.6 Hz), 5.17 (1H, dq, *J* = 10.4, 1.6 Hz), 4.42 (1H, dd, *J* = 7.5, 5.5 Hz), 3.97 (2H, dt, *J* = 5.7, 1.4 Hz), 3.43 (2H, t, *J* = 6.7 Hz), 1.73-1.26 (12H, m); ^{13}C-NMR ($CDCl_3$, 125 MHz, δ): 170.9 (C=O), 141.8 (C), 135.0 (CH), 127.3 (CH_2), 116.9 (CH_2), 71.8 (CH_2), 71.6 (CH), 70.4 (CH_2), 36.1 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 25.7 (CH_2); IR (cm^{-1}): 3358, 2932, 2856, 1695, 1627, 1245; MS-ESI: 279 $[M+Na]^+$; HRMS ES^+: $[M+Na]^+$ calcd for $C_{14}H_{24}NaO_4$, 279.1567, found, 279.1566.

Methyl 3-hydroxy-2-methylenetridec-12-enoate (24b)

10-Undecen-al (3.00 g, 17.8 mmol) was dissolved in methyl acrylate (1.29 mL, 14.3 mmol) then MeOH (450 μL) and DABCO (280 mg, 2.50 mmol) were added and the solution stirred for 7 days. The volatiles were removed and the product purified by column chromatography (20% EtOAc in petroleum ether) to give **24b** (1.91 g, 53%) as an oil. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.17 (1H, s), 5.83-5.69 (2H, m), 4.35 (1H, d, *J* = 5.9 Hz), 3.73 (3H, s), 2.80 (1H, s), 1.99 (2H, q, *J* = 7.1 Hz), 1.64-1.52 (2H, m), 1.44-1.20 (12H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 167.0 (C=O), 142.7 (C), 139.1 (CH), 124.8 (CH_2), 114.1 (CH_2), 71.4 (CH), 51.8 (CH_3), 36.3 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 25.8 (CH_2); IR (cm^{-1}): 3430, 2926, 2854, 1719, 1627; MS-ESI 277 $[M+Na]^+$; HRMS ES^+ $[M+Na]^+$ calcd for $C_{15}H_{26}NaO_3$, 277.1774; found, 277.1772.

3-Hydroxy-2-methylenetridec-12-enoic acid (9b)

To **24b** (1.91 g, 7.51 mmol) dissolved in THF (20 mL). $LiOH·H_2O$ (1.50 g, 35.7 mmol) in H_2O (20 mL) was added and the solution stirred for 18 h. The layers were separated and the aqueous layer acidified to pH 1 with 2N HCl and extracted with EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed, to give **9b** (1.80 g, 100%) as a colourless oil, which was used without further purification. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.88 (1H, br s), 6.37 (1H, s), 5.90 (1H, s), 5.79 (1H, ddd, *J* = 16.8, 10.1, 5.0 Hz), 5.01-4.94 (1H, m), 4.94-4.89 (1H, m), 4.42 (1H, t, *J* = 5.9 Hz), 2.02 (2H, q, *J* = 6.4 Hz), 1.74-1.57 (2H, m), 1.46-1.26 (12H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 171.2 (C=O), 141.9 (C), 139.2 (CH), 127.4 (CH_2), 114.1 (CH_2), 71.5 (CH), 36.1 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.39 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.8 (CH_2); IR (cm^{-1}): 3500, 2924, 2854, 1693, 1627; MS-ESI 263 $[M+Na]^+$.

10-(Allyloxy)-3-hydroxy-N-ethyl-2-methylenedecanamide (10a)

To a solution of **9a** (421 mg, 1.64 mmol) in EtOH (16 mL) were added NMM (0.4 mL, 3.64 mmol), HOBt (88%, 40 mg, 0.26 mmol) and $EtNH_2$ (2 M in THF, 0.82 mL, 1.64 mmol). The solution was cooled to 5 °C, EDC·HCl (378 mg, 1.97 mmol) added then allowed to warm to room temperature and stirred for 16 h. The resulting mixture was diluted with EtOAc (20 mL) and H_2O (10 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (45% EtOAc + 1% Et_3N in petroleum ether) gave **10a** (339 mg, 73%). M.p. 55-58 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.51 (1H, br s), 5.92 (1H, ddt, *J* = 17.5, 10.4, 5.6 Hz), 5.74 (1H, s), 5.41 (1H, s), 5.27 (1H, dq, *J* = 17.4, 1.6 Hz), 5.16 (1H, dt, *J* = 10.4, 1.6 Hz), 4.32 (1H, q, *J* = 6.3 Hz), 3.96 (2H, dt, *J* = 5.7, 1.5 Hz), 3.41 (2H, t, *J* = 6.7 Hz), 3.38-3.32 (2H, m), 3.23-3.10 (1H, br s), 1.73-1.53 (4H, m), 1.48-1.26 (8H, m), 1.18 (3H, t, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 167.9 (C=O), 145.8 (C), 135.1 (CH), 119.3 (CH_2), 116.7 (CH_2), 74.1 (CH), 71.8 (CH_2), 70.5 (CH_2), 35.7 (CH_2), 34.3 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 14.8 (CH_3); IR (cm^{-1}): 3321, 2928, 2851, 1619, 1537, 1245; MS-ESI: 283 $[M+H]^+$, 306 $[M+Na]^+$; HRMS: ES^+ $[M+Na]^+$ calcd for $C_{16}H_{29}NNaO_3$, 306.2040; found, 306.2042.

2-(4-Ethylcarbamoyl)-10-(allyloxy)dec-1-en-3-yl methanesulfonate (25)

A solution of **10a** (339 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C. Et_3N (0.30 mL, 2.15 mmol) was added followed by MsCl (0.20 mL, 2.58 mmol) dropwise. The reaction was stirred at –78 °C for 4 h then quenched by addition of H_2O (5 mL). The organic layer was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography (50% EtOAc in petroleum ether) yielded **25** (363 mg, 84%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.01 (1H, br s), 5.95-5.86 (1H, m), 5.80 (1H, d, *J* = 1.5 Hz), 5.66 (1H, d, *J* = 1.5 Hz), 5.37 (1H, t, *J* = 6.6 Hz), 5.26 (1H, dq, *J* = 17.3, 1.7 Hz), 5.16 (1H, dq, *J* = 10.4, 1.7 Hz), 3.95 (2H, d, *J* = 5.7 Hz), 3.41 (2H, t, *J* = 6.8 Hz), 3.38-3.26 (2H, m), 3.00 (3H, s), 1.91-1.80 (2H, m), 1.64-1.50 (2H, m), 1.32 (8H, m), 1.18 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 166.2 (C=O), 143.6 (C), 135.1 (CH), 120.2 (CH_2), 116.7 (CH_2), 81.4 (CH), 71.8 (CH_2), 70.4 (CH_2), 38.5 (CH_3), 35.0 (CH_2), 34.6 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.1 (CH_2), 25.2 (CH_2), 14.7 (CH_3); IR (cm^{-1}): 3337, 2933, 2858, 1660, 1536, 1454, 1352, 1173; MS-ESI: 362 $[M+H]^+$, 384 $[M+Na]^+$; HRMS ES^+: calcd for $C_{17}H_{31}NNaO_5S$ 384.1815; found, 384.1805.

4-(7-(Allyloxy)heptyl)-1-ethyl-3-methyleneazetidin-2-one (11a)

Mesylate **25** (363 mg, 1.00 mmol) was dissolved in THF (10 mL) and cooled to –15 °C. KO^{t}Bu (123 mg, 1.10 mmol) was added in one portion then the mixture stirred for 3.5 h at –15 °C. The solution was diluted with Et_2O (10 mL) and quenched by addition of NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure. Column chromatography (40% EtOAc in petroleum ether) gave **11a** (85 mg, 32%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.00-5.85 (1H, m), 5.61 (1H, d, *J* = 1.5 Hz), 5.27 (1H, dq, *J* = 17.2, 1.6 Hz), 5.17 (1H, dq, *J* = 10.6, 1.6 Hz), 5.09 (1H, d, *J* = 1.5 Hz), 4.05 (1H, t, *J* = 5.8 Hz), 3.96 (2H, d, *J* = 5.8 Hz), 3.59-3.47 (1H, m), 3.43 (2H, t, *J* = 6.6 Hz), 3.24-3.09 (1H, m), 1.85-1.71 (1H, m), 1.67-1.50 (3H, m), 1.45-1.29 (8H, m), 1.18 (3H, t, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 163.0 (C=O), 149.9 (C), 135.2 (CH), 116.8 (CH_2), 107.9 (CH_2), 71.9 (CH_2), 70.5 (CH_2), 59.9 (CH), 35.4 (CH_2), 32.0 (CH_2), 29.83 (CH_2), 29.76 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.3 (CH_2), 13.5 (CH_3); IR (cm^{-1}): 2929, 2856, 1746, 1457, 1222; MS-ESI: 288 [M+Na]$^+$; HRMS ES$^+$: [M+Na]$^+$ calcd for $C_{16}H_{27}NNaO_2$, 288.1934; found, 288.1938.

10-(Allyloxy)-3-hydroxy-N-(4-methoxyphenyl)-2-methylene-decanamide (12a)

A solution of **9a** (3.68 g, 14.4 mmol) and *p*-anisidine (1.77 g, 14.4 mmol) in CH_2Cl_2 (300 mL) was cooled to 0 °C. DCC (2.96 g, 14.4 mmol) was added portionwise over 10 minutes and the solution allowed to warm to room temperature over 16 h. The resulting mixture was filtered through Celite, washed with CH_2Cl_2 and the filtrate concentrated under reduced pressure. Column chromatography (33% EtOAc in petroleum ether) gave **12a** (3.96 g, 76%) as a white solid. M.p. 74-76 °C ($CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 8.55 (1H, s), 7.49 (2H, d, *J* = 8.8 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 6.01 (1H, s), 5.98-5.85 (1H, m), 5.53 (1H, s), 5.26 (1H, d, *J* = 17.3 Hz), 5.17 (1H, d, *J* = 10.6 Hz), 4.41 (1H, t, *J* = 6.6 Hz), 3.96 (2H, d, *J* = 5.3 Hz), 3.80 (3H, s), 3.41 (3H, t, *J* = 6.6 Hz), 1.79-1.61 (2H, m), 1.61-1.50 (2H, m), 1.45-1.24 (8H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 165.3 (C=O), 156.5 (C), 145.5 (C), 135.1 (CH), 131.0 (C), 122.0 (2 x CH), 121.8 (CH_2), 116.9 (CH_2), 114.3 (2 x CH), 74.3 (CH), 71.9 (CH_2), 70.6 (CH_2), 55.6 (CH_3), 35.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 26.0 (CH_2); IR (cm^{-1}): 3293, 2925, 2853, 1511, 1509, 1245, 827; MS-ESI: 384 [M+Na]$^+$; HRMS ES$^+$: [M+Na]$^+$ calcd for $C_{21}H_{31}NNaO_4$, 384.2145, found, 384.2149.

2-(4-Methoxyphenylcarbamoyl)-10-(allyloxy)dec-1-en-3-yl methanesulfonate (26a)

A solution of **12a** (3.86 g, 10.7 mmol) in CH_2Cl_2 (100 mL) was cooled to -78 °C. Et_3N (2.98 mL, 21.4 mmol) was added, followed by MsCl (1.65 mL, 21.4 mmol) dropwise. After 4 h at -78 °C, the reaction was quenched with H_2O (20 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography (30% EtOAc in petroleum ether) gave **26a** (4.34 g, 92%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 7.72 (1H, s), 7.46 (2H, d, *J* = 8.6 Hz), 6.88 (2H, d, *J* = 8.6 Hz), 5.95 (1H, s), 5.97-5.85 (1H, m), 5.78 (1H, s), 5.42 (1H, t, *J* = 6.5 Hz), 5.26 (1H, d, *J* = 17.2 Hz), 5.17 (1H, d, *J* = 10.3 Hz), 3.96 (2H, d, *J* = 5.4 Hz), 3.80 (3H, s), 3.41 (2H, t, *J* = 6.6 Hz), 3.04 (3H, s), 1.98-1.87 (2H, q, *J* = 7.1 Hz), 1.63-1.51 (2H, m), 1.52-1.22 (8H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 164.5 (C=O), 156.9 (C), 144.1 (C), 135.2 (CH), 130.6 (C), 122.1 (CH), 121.1 (CH_2), 116.9 (CH_2), 114.3 (CH), 81.4 (CH), 71.9 (CH_2), 70.5 (CH_2), 55.6 (CH_3), 38.7 (CH_3), 35.1 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 26.2 (CH_2), 25.4 (CH_2); IR (cm^{-1}): 3358, 2933, 2856, 1666, 1510, 1509, 1349, 1245, 1170, 827; MS-ESI: 440 [M+H]$^+$, 462 [M+Na]$^+$; HRMS ES$^+$: [M+Na]$^+$ calcd for $C_{22}H_{33}NNaO_6S$ 462.1921; found, 462.1937.

4-(7-(Allyloxy)heptyl)-1-(4-methoxyphenyl)-3-methylene-azetidin-2-one (13a)

Mesylate **26a** (4.28 g, 9.74 mmol) was dissolved in THF (120 mL) and cooled to -15 °C. KO^{t}Bu (1.20 g, 10.7 mmol) was added in one portion and the solution stirred at -15 °C for 0.5 h. The reaction was quenched with saturated NH_4Cl solution (50 mL), the layers separated, and the aqueous layer extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in petroleum ether) gave **13a** (2.53 g, 76%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 7.36 (2H, d, *J* = 8.2 Hz), 6.90 (2H, d, *J* = 8.2 Hz), 5.97-5.85 (1H, m), 5.78 (1H, br s), 5.27 (1H, d, *J* = 14.1 Hz), 5.25 (1H, br s), 5.17 (1H, d, *J* = 10.4 Hz), 4.55-4.47 (1H, m), 3.94 (2H, dt, *J* = 5.5, 1.7 Hz), 3.78 (3H, s), 3.39 (2H, d, *J* = 6.6 Hz), 2.06-1.95 (1H, m), 1.84-1.72 (1H, m), 1.61-1.50 (2H, m), 1.47-1.23 (8H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 160.2 (C=O), 156.3 (C), 148.6 (C), 135.2 (CH), 131.2 (C), 118.5 (CH), 116.8 (CH_2), 114.6 (CH), 109.5 (CH_2), 71.9 (CH_2), 70.5 (CH_2), 60.5 (CH), 55.6 (CH_3), 30.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 24.4 (CH_2); IR (cm^{-1}): 2931, 2856, 1739, 1510, 1246, 827; MS-ESI: 344 [M+H]$^+$, 366 [M+Na]$^+$; HRMS ES$^+$: [M+Na]$^+$ calcd for $C_{21}H_{29}NNaO_3$, 366.2040; found, 366.2036.

3-Hydroxy-*N*-(4-methoxyphenyl)-2-methylenetridec-12-enamide (12b)

9b (900 mg, 3.74 mmol) and *p*-anisidine (461 mg, 3.74 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. DCC (772 mg, 3.74 mmol) in CH_2Cl_2 (50 mL) was added slowly and the solution allowed to warm to room temperature over 18 h. The resulting suspension was filtered through Celite, washed with CH_2Cl_2, and the filtrate concentrated under reduced pressure. Column chromatography (30% EtOAc in petroleum ether) gave **12b** (688 mg, 53%) as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ): 8.54 (1H, br s), 7.50-7.43 (2H, m), 6.89-6.81 (2H, m), 5.99 (1H, s), 5.78 (1H, ddt, *J* = 16.8, 10.3, 6.6 Hz), 5.50 (1H, s), 5.02-4.86 (2H, m), 4.43 (1H, q, *J* = 6.4 Hz), 3.78 (3H, s), 2.72 (1H, d, *J* = 4.7 Hz), 1.96 (2H, q, *J* = 6.6 Hz),

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1.85-1.60 (2H, m), 1.50-1.16 (12H, m); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ): 164.5 (C=O), 156.2 (C), 145.2 (C), 138.6 (CH), 130.1 (C), 121.3 (CH), 120.8 (CH_2), 113.8 (CH), 113.7 (CH_2), 73.7 (CH), 54.9 (CH_3), 35.1 (CH_2), 33.2 (CH_2), 29.5 (CH_2), 29.41 (CH_2), 29.36 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.8 (CH_2); IR (cm^{-1}): 3283, 2925, 2853, 1511, 1246, 828; MS-ESI: 346 $[M+H]^+$, 368 $[M+Na]^+$; HRMS ES^+: $[M+Na]^+$ calcd for $C_{21}H_{31}NNaO_3$, 368.2196, found, 368.2198.

2-(4-Methoxyphenylcarbamoyl)trideca-1,12-dien-3-yl methanesulfonate (26b)

A solution of **12b** (688 mg, 1.99 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C. Et_3N (550 μL, 3.95 mmol) was added followed by MsCl (300 μL, 3.88 mmol) dropwise. After 2 h, the reaction was quenched with H_2O (10 mL) and allowed to warm to room temperature. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in petroleum ether) gave **26b** (816 mg, 97%) as an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ): 7.70 (1H, br s), 7.49-7.41 (2H, m), 6.90-6.83 (2H, m), 5.94 (1H, s), 5.87-5.71 (2H, m), 5.41 (1H, t, *J* = 6.6 Hz), 5.03-4.88 (2H, m), 3.79 (3H, s), 3.02 (3H, s), 2.05-1.97 (2H, m), 1.91 (2H, q, *J* = 7.5 Hz), 1.48-1.22 (12H, m); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ): 164.5 (C=O), 157.0 (C), 144.2 (C), 139.3 (CH), 130.6 (C), 122.1 (CH), 121.4 (CH_2), 114.4 (CH), 114.3 (CH_2), 81.5 (CH), 55.6 (CH_3), 38.7 (CH_3), 35.1 (CH_2), 33.9 (CH_2), 29.5 (2 x CH_2), 29.2 (2 x CH_2), 29.0 (CH_2), 25.5 (CH_2); IR (cm^{-1}): 3358, 2926, 2854, 1663, 1511, 1351, 1245, 1173, 827; MS-ESI: 424 $[M+H]^+$, 446 $[M+Na]$; HRMS: ES^+ $[M+H]^+$ calcd for $C_{22}H_{33}NNaO_5S$, 446.1972; found, 446.1967.

4-(Dec-9-enyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (13b)

Mesylate **26b** (230 mg, 0.54 mmol) was dissolved in THF (10 mL) and cooled to –15 °C. KO^{t}Bu (60 mg, 0.54 mmol) was added in one portion and the mixture stirred for 2 h at –15 °C. The reaction was quenched with sat. NH_4Cl (10 mL), the organic layer was separated and extracted with Et_2O (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was purified by column chromatography (5% EtOAc in petroleum ether) to give **13b** (111 mg, 63%). ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 7.42-7.31 (2H, m), 6.97-6.83 (2H, m), 5.86-5.74 (2H, m), 5.24 (1H, d, *J* = 1.3 Hz), 4.98 (1H, dq, *J* = 17.1, 1.8 Hz), 4.95-4.90 (1H, m), 4.52 (1H, d, *J* = 7.0 Hz), 3.80 (3H, s), 2.12-1.93 (3H, m), 1.89-1.72 (1H, m), 1.49-1.17 (12H, m); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ): 164.3 (C=O), 155.6 (C), 147.9 (C), 138.6 (CH), 130.5 (C), 117.8 (CH), 113.9 (CH), 113.5 (CH_2), 108.8 (CH), 59.8 (CH), 54.9 (CH_3), 33.2 (CH_2), 30.1 (CH_2), 28.94 (CH_2), 28.88 (CH_2), 28.7 (2 x CH_2), 28.5 (CH_2), 28.2 (CH_2); IR (cm^{-1}): 2925, 2853, 1727, 1509, 1245, 827; MS-ESI: 328 $[M+H]^+$, 350 $[M+Na]^+$; HRMS: ES^+ $[M+H]^+$ calcd for $C_{21}H_{29}NO_2$, 328.2271; found, 328.2277.

***tert*-Butyl-3-methylidene-2-oxo-4-[7-(prop-2-en-1-yloxy)heptyl]-azetidine-1-carboxylate (14a)**

A solution of CAN (3.83 g, 6.99 mmol) in H_2O (80 mL) was added dropwise to a stirred solution of **13a** (800 mg, 2.33 mmol) in MeCN (80 mL) at 0 °C. After 2 h, the mixture was diluted with Et_2O (100 mL) and sat. $NaHCO_3$ (100 mL) added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in MeCN (40 ml) and cooled to 0 °C. Boc_2O (1.02 g, 4.66 mmol) and DMAP (32 mg, 0.261 mmol) were added, and the reaction mixture was stirred at room temperature for 16 h. CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ solution (100 mL) were added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography (20% EtOAc in petroleum ether) gave **14a** (493 mg, 63% over 2 steps) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 5.95 (1H, s), 5.98-5.86 (1H, m), 5.39 (1H, s), 5.27 (1H, d, *J* = 17.3 Hz), 5.17 (1H, d, *J* = 10.4 Hz), 4.44-4.38 (1H, m), 3.96 (2H, d, *J* = 5.5 Hz), 3.42 (2H, t, *J* = 6.6 Hz), 2.06-1.94 (1H, m), 1.80-1.66 (1H, m), 1.60-1.53 (2H, m), 1.53 (9H, s), 1.42-1.28 (8H, m); ^{13}C-NMR ($CDCl_3$, 125 MHz, δ): 159.9 (C), 148.7 (C), 147.8 (C), 135.1 (CH), 116.7 (CH_2), 114.4 (CH_2), 83.1 (C), 71.8 (CH_2), 70.4 (CH_2), 60.5 (CH), 31.5 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.1 (CH_3), 26.1 (CH_2), 24.6 (CH_2); IR (cm^{-1}) 1797, 1717, 1458, 1332, 1147: MS-ESI: 360 $[M+Na]^+$; HRMS: ES^+ $[M+Na]^+$ calcd for $C_{19}H_{31}NNaO_4$, 360.2145; found, 360.2145.

(Z)-14-(4-Methoxyphenyl)-9-oxa-14-aza-bicyclo[10.2.0]-tetradec-11-en-13-one (19) and (1Z,14Z)-12,25-bis(4-methoxyphenyl)-12,25-diazatricyclo[22.2.0.011,14]hexacosa-1,14-diene-13,26-dione) (20)

To **13a** (20 mg, 0.058 mmol) in CH_2Cl_2 (233 mL) was added **16** (5 mg, 0.0058 mmol) and the solution heated at reflux for 24 h. On cooling, the solvent was removed under reduced pressure. Column chromatography (20-30% EtOAc in petroleum ether) yielded less polar **19** (8 mg, 44%) as an 8:1 mixture of *Z*:*E* isomers. ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 7.46-7.33 (2H, m), 6.92-6.83 (2H, m), 5.97 (1H, dd, *J* = 10.8, 4.1 Hz), 4.69 (1H, dd, *J* = 12.8, 10.8 Hz), 4.57 (1H, dd, *J* = 6.4, 3.6 Hz), 4.19 (1H, dd, *J* = 12.8, 4.2 Hz), 3.82 (3H, s), 3.75 (1H, ddd, *J* = 10.8, 6.4, 4.2 Hz), 3.52 (1H, ddd, *J* = 11.2, 7.4, 4.2 Hz), 2.11-2.00 (1H, m), 1.97-1.89 (1H, m), 1.62-1.28 (10H, m); ^{13}C-NMR ($CDCl_3$, 125 MHz, δ): 160.0 (C=O), 156.2 (C), 142.8 (C), 131.2 (C), 126.8 (CH), 126.7 (CH), 118.3 (CH), 114.6 (CH), 68.0 (CH_2), 65.0 (CH_2), 59.2 (CH), 55.5 (CH_3), 28.5 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 24.3 (CH_2), 22.0 (CH_2); IR (cm^{-1}): 2918, 2852, 1728, 1512, 1246, 830; MS-ESI: 316 $[M+H]^+$, 338 $[M+Na]^+$; HRMS: ES^+ $[M+H]^+$ calcd for $C_{19}H_{26}NO_3$, 316.1907; found, 316.1911 $[M+Na]^+$ calcd for $C_{19}H_{25}NNaO_3$, 338.1727; found, 338.1728. Further elution provided more polar *Z*,*Z*-**20** (3 mg, 17%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.40-7.30 (4H, m), 6.97-6.80 (4H, m), 5.83 (2H, ddd, *J* = 8.4, 5.4, 2.4 Hz), 4.58 (2H, ddd, *J* = 21.4, 13.1, 8.4 Hz), 4.50-4.43 (2H, m), 4.36 (2H, ddd, *J* = 21.4, 13.1, 5.4 Hz), 3.80 (6H, s), 3.57-3.43 (4H, m),

2.08-1.96 (2H, m), 1.85-1.69 (2H, m), 1.65-1.27 (20H, m); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 159.84 (C=O), 159.78 (C=O), 156.2 (C), 141.8 (C), 131.15 (C), 131.10 (C), 126.62 (CH), 126.55 (CH), 118.2 (4 x CH), 114.6 (4 x CH), 70.40 (CH_2), 70.32 (CH_2), 66.48 (CH_2), 66.42 (CH_2), 59.3 (CH), 55.5 (CH_3), 30.8 (CH_2), 30.7 (CH_2), 29.94 (CH_2), 29.89 (CH_2), 29.66 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.97 (CH_2), 25.94 (CH_2), 24.0 (CH_2), 23.9 (CH_2); IR (cm^{-1}): 2931, 2856, 1733, 1509, 1298, 829; MS-ESI: 631 $[M+H]^+$, 653 $[M+Na]^+$; HRMS: ES$^+$ $[M+H]^+$ calcd for $C_{38}H_{51}N_2O_6$, 631.3742; found, 631.3750, $[M+Na]^+$ calcd for $C_{38}H_{50}N_2NaO_6$, 653.3561; found, 653.3567

(*Z*)-12-(4-methoxyphenyl)-12-azabicyclo[9.2.0]tridec-1-en-13-one (21) and (1*Z*,14*Z*)-12,25-bis(4-methoxyphenyl)-12,25-diazatricyclo[22.2.0.011,14]hexacosa-1,14-diene-13,26-dione) (22)

To **13b** (62 mg, 0.19 mmol) in CH_2Cl_2 (95 mL) was added **16** (15 mg, 0.018 mmol) and the solution heated at reflux for 24 h. On cooling, the solvent was removed under reduced pressure. Column chromatography (10-20% EtOAc in petroleum ether) yielded **21** (3 mg, 6%) as a crystalline solid. M.p. 155-160 °C (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 600 MHz, δ): 7.45-7.34 (2H, m), 6.96-6.81 (2H, m), 5.71 (1H, dd, *J* = 12.0, 4.4 Hz), 4.52 (1H, d, *J* = 5.1 Hz), 3.79 (3H, s), 2.81-2.74 (1H, m), 2.30-2.15 (2H, m), 2.05-1.94 (1H, m), 1.94-1.83 (1H, m), 1.70-1.14 (11H, m); ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 161.5 (C=O), 155.8 (C), 139.3 (C), 132.6 (C) 131.8 (CH), 117.5 (CH), 114.5 (CH), 58.8 (CH), 55.5 (CH_3), 29.4 (CH_2), 27.4 (CH_2), 27.0 (CH_2), 25.60 (CH_2), 25.57 (CH_2), 25.0 (CH_2), 22.3 (CH_2), 20.7 (CH_2); IR (cm^{-1}): 2925, 2853, 1731, 1511, 1246, 829; MS-ESI: 300 $[M+H]^+$, 322 $[M+Na]^+$; HRMS: ES$^+$ $[M+H]^+$ calcd for $C_{19}H_{26}NO_2$, 300.1958; found, 300.1958. Further elution provided more polar **22** (11 mg, 20%) as a crystalline solid. M.p. 149-155 °C (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 7.31-7.23 (4H, m), 6.84-6.77 (4H, m), 5.52 (2H, dt, *J* = 11.0 Hz, 4.5 Hz), 4.44-4.39 (2H, m), 3.72 (6H, s), 2.95-2.81 (2H, m), 2.17-2.07 (2H, m), 1.94-1.81 (2H, m), 1.80-1.67 (2H, m), 1.38-1.02 (24H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 161.6 (C=O), 161.0 (C=O), 156.0 (2 x C), 139.6 (C), 139.4 (C), 131.9 (C), 131.8 (C), 131.0 (CH), 130.7, 118.1 (2 x CH), 118.0 (2 x CH), 114.6 (4 x CH), 59.42 (CH), 59.36 (CH), 55.6 (2 x CH_3), 30.3 (CH_2), 30.14 (CH_2), 30.08 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.30 (CH_2), 29.27 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.54 (CH_2), 28.48 (CH_2), 23.1 (CH_2), 22.8 (CH_2); IR (cm^{-1}): 2920, 2849, 1712, 1509, 1246, 826; MS-ESI: 599 $[M+H]^+$, 621 $[M+Na]^+$; HRMS: ES$^+$ $[M+H]^+$ calcd for $C_{38}H_{51}N_2O_4$, 599.3843; found, 599.3850.

(Z)-13-Ethyl-4-oxa-13-azabicyclo[10.2.0]tetradec-1-en-14-one (23)

To *Z*-**19** (19 mg, 0.06 mmol) in MeCN (2 mL) at 0 °C was added CAN (99 mg, 0.18 mmol) in H_2O (2 mL) dropwise. The reaction was stirred for 1 h at 0 °C, then poured into Et_2O (5 mL) and sat. $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase further extracted with Et_2O (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. Column chromatography (50% EtOAc in petroleum ether) gave (Z)-4-oxa-13-azabicyclo[10.2.0]tetradec-1-en-14-one (5 mg, 0.023 mmol), which used immediately in the next step. This material was dissolved in ethyl iodide (5 mL) and KOH (5 mg, 0.096 mmol) added. The mixture was stirred for 18 h at room temperature then poured into H_2O (5 mL). The layers were separated and the aqueous extracted with Et_2O (2 x 5 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Semi-preparative HPLC (40% H_2O in MeCN, flow rate 1.0 mL min^{-1}) yielded **23** (3 mg, 21% over two steps) as an oil . ^{1}H-NMR ($CDCl_3$, 700 MHz, δ): 5.77 (1H, dd, *J* = 10.5, 3.9 Hz), 4.54 (1H, dd, *J* = 12.7, 10.5 Hz), 4.17-4.06 (2H, m), 3.68 (1H, dt, *J* = 10.5, 5.4 Hz), 3.56-3.47 (1H, m), 3.44 (1H, dt, *J* = 11.3, 5.4), 3.19-3.08 (1H, m), 1.89-1.80 (1H, m), 1.71-1.63 (2H, m), 1.52-1.48 (2H, m), 1.45-1.26 (7H, m), 1.19 (3H, t, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 175 MHz, δ): 163.1 (C=O), 143.7 (C), 125.2 (CH), 67.3 (CH_2), 65.3 (CH_2), 58.1 (CH), 34.8 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 21.9 (CH_2), 20.4 (CH_2), 13.4 (CH_3); IR (cm^{-1}): 2928, 2856, 1738, 1395, 1220; MS-ESI: 260 $[M+Na]^+$; HRMS: ES$^+$ $[M+Na]^+$ calcd for $C_{14}H_{23}NNaO_2$, 260.1621; found, 260.1617.

Acknowledgements

We thank EPSRC (EP/K031783/1) and the University of Warwick for financial support. The Oxford Diffraction Gemini XRD system was obtained, through the Science City Advanced Materials project: Creating and Characterizing Next Generation Advanced Materials.

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† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra for **9-15** and **19-23**; HPLC traces for RCM equilibration; X-ray depiction of **21**, herbicidal assays and DFT methods. See DOI: 10.1039/b000000x/

‡ CCDC 1048609 crystal data: **19**, $C_{19}H_{25}NO_3$ (*M* =315.40): monoclinic, space group P2(1)/n, *a* = 6.2083(2) Å, *b* = 12.6788(5) Å, *c* = 21.0520(9) Å, *α* = 90°, *β* = 91.476(3)°, *γ* = 90°, *V* = 1656.54(12) Å^3, *Z* = 4, *T* = 150(2) K, μ(MoKα) = 0.085 mm^{-1}, *Dcalc* = 1.265 g/mm^3, 15927 reflections measured (6.426° ≤ 2Θ ≤ 60.578°), 4458 unique (R_{int} = 0.0644, R_{sigma} = 0.0694) which were used in all calculations. The final R_1 was 0.0781 (I > 2σ(I)) and wR_2 was 0.1385 (all data). CCDC 1048610 crystal data: **20**, $C_{38}H_{50}N_2O_6$ (*M* =630.80): triclinic, space group P-1 (no. 2), *a* = 8.7440(3) Å, *b* = 10.4501(4) Å, *c* = 20.1688(6) Å, *α* = 100.027(3)°, *β* = 98.395(3)°, *γ* = 104.657(3)°, *V* = 1720.46(10) Å^3, *Z* = 2, *T* = 150(2) K, μ(Cu Kα) = 0.653 mm^{-1}, *Dcalc* = 1.218 g/mm^3, 12402 reflections measured (8.968 ≤ 2Θ ≤ 156.368), 7138 unique (R_{int} = 0.0246, R_{sigma} = 0.0315) which were used in all calculations. The final R_1 was 0.0417 (I > 2σ(I)) and wR_2 was 0.1229 (all data). CCDC 1048608 crystal

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data: **21**, $C_{19}H_{25}NO_2$, (M =299.40): monoclinic, space group C2/c, a = 20.3839(14) Å, b = 6.2114(3) Å, c = 25.5110(16) Å, α = 90°, β = 97.442(6)°, γ = 90°, V = 3202.8(3) Å^3, Z = 8, T = 100(2) K, μ(MoKα) = 0.626 mm^{-1}, *Dcalc* = 1.242 g/mm^3, 8160 reflections measured (6.988° ≤ 2Θ ≤ 141.822°), 3030 unique (R_{int} = 0.0619, R_{sigma} = 0.0557) which were used in all calculations. The final R_1 was 0.0649 (I > 2σ(I)) and wR_2 was 0.1856 (all data).

§ The very low yields make it difficult to discount the possibility that quantities of *E*-**21** were also produced. However, DFT calculations conducted on both stereoisomers of **21** indicate that the *Z*-isomer is more stable by 4.6 kJ mol^{-1} (see Supplementary Information).

¶ This trend was seen at intermediate concentrations: *Z* : *E* = 1.6:1 [2 mM]; 2.3:1 [1 mM]; 3.9:1 [0.5 mM]; >8:1 [0.25 mM]).

¥ For glyphosate, ED_{50} = 43.1±4.3 μM. Unfortunately, the poor solubility of *Z*-**23** prevented determination of this parameter for the synthetic derivative.

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